IL MIO…CLONO POST-ANOSSICO
“GEMELLI DIVERSI?”

MERCOLEDI’ 12 FEBBRAIO 2014 0RE 14:30

DOTT. ELGHOUTY EYAD
DOTT.SSA ELISABETTA PECCI
DOTT.SSA ELISA SEGHELINI

- Survivors of cardic arrest have a high incidence of neurological injury.
- A report from the Ontario Prehospital Advanced Life Support (OPALS) study indicate that 12.5% of survivors of cardic arrest ha moderate or severe neurological impairment.
- Accurate prediction of neurological function following cardic arrest is difficult.
- Accurate prediction of neurological outcome following cardic arrest is necessary to guide medical management and to guide discussion with the patient's relatives.

Caso clinico

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 908–911 doi:10.1111/j.1365-2044.2009.05939.x

CASE REPORT

Myoclonus after cardiac arrest: pitfalls in diagnosis and prognosis*

W. A. English,[1,†] N. J. Giffin[2] and J. P. Nolan[3]

1 Specialist Registrar, Department of Anaesthesia and Critical Care, 2 Consultant, Department of Neurology, 3 Consultant, Department of Anaesthesia and Critical Care, Royal United Hospital, Bath, UK

Caso clinico

- Uomo di 44 anni si presenta con un edema rapidamente progressivo della testa e del collo associato a dispnea ingravescente.
- APR: Obesità patologica (BMI 52) – Ipertensione arteriosa.
- Terapia domiciliare: Losartan
- Sospetto diagnostico: Angioedema secondario a Losartan.

- Medicamenti: 5 mg di adrenalina per aerosol – 200 mg di idrocortisone ev – 10 mg di clorfenamina ev.
- Sviluppa un quadro di ostruzione delle vie aeree
- Impossibilità all'intubazione OT per edema delle vie aeree; si procede a tracheotomia chirurgica d'emergenza; tecnica difficoltosa per obesità ed edema pretracheale.
- La procedura è complicata da arresto cardiocircolatorio con PEA. Iniziata CRP immediatamente ma senza adeguata ventilazione fino al posizionamento di accesso tracheale d'emergenza.
- Ritorno alla circolazione spontanea (ROSC) dopo 3 minuti dall'arresto.

- Ricovero in ICU: sedazione con propofol e alfentanil e ventilazione meccanica.
- A 22 ore dall'ammissione: in corso di sedazione, prima crisi tonico-clonica della durata di 2 min. regredita con la somministrazione di 2 mg di Lorazepam.

Terapia antiepilettica con dose carico di fenotoina 1.5 g e quindi 300 mg tre volte al giorno.

- A 56 ore: in sedazione, comparsa di primo episodio di attività mioclonica.

Aggiunta terapia con Valproato di sodio 1 gr x 2 e Clonazepam 1 mg.

- A 70 ore: comparsa di scosse miocloniche persistenti subentranti a 2 min. dalla sospensione delle sedazioni con propofol.

EEG non conferma lo stato mioclonico ma mostra frequenti punte multiple miocloniche.

Inizia terapia Levetiracetam 1 gr x 2 al giorno e potenziata la terapia con Valproato di sodio a 1.25 gr x 2 e Clonazepam a 1 mg x 4 al giorno in previsione della sospensione di propofol.

- A 5 giorni dall'ammissione, le sedazioni con propofol vengono sospese:
  - Persiste mioclono intermittente
  - Accentuazione del mioclono all'esecuzione dei comandi (intention myoclonus).

- Dimesso dall'ICU dopo 30 giorni svezzato da ventilatore e con GCS di 15.

- Muore a 54 giorni dall'ammissione per polmonite.

SEMPRE LO STESSO MIOCLONO NEL PAZIENTE PRIMA IN COMA E POI SVEGLIO?

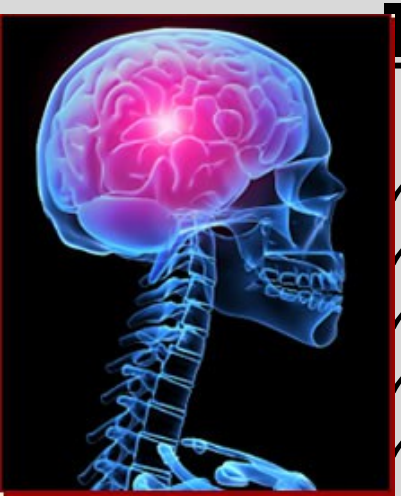
MIOCLONO DIFFERENTE?

MIOCLONO

IMPROVVISE E *RAPIDE*
CONTRAZIONI MUSCOLARI A SCATTO
CON AMPIEZZA VARIABILE
E
A PARTENZA DAL SISTEMA NERVOSO

CLASSIFICAZIONE:

- ✓ corticale
- ✓ cortico-sottocorticale
- ✓ subcorticale-non segmentale
- ✓ segmentale
- ✓ periferico



INDAGINI STRUMENTALI

- ✓ EEG
- ✓ EMG
- ✓ EEG-EMG poligrafia
- ✓ PESS
- ✓ Risposta EMG alla stimolazione

Neurotherapeutics
DOI 10.1007/s13311-013-0216-3

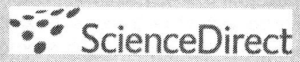
REVIEW

Treatment of Myoclonus

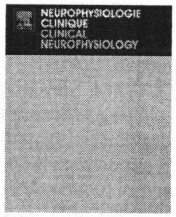
John N. Caviness

Neurophysiologie Clinique 36 (2006) 309-318

available at www.sciencedirect.com



journal homepage: http://france.elsevier.com/direct/neucli



ORIGINAL ARTICLE / ARTICLE ORIGINAL

Symptomatic myoclonus

Myoclonies symptomatiques

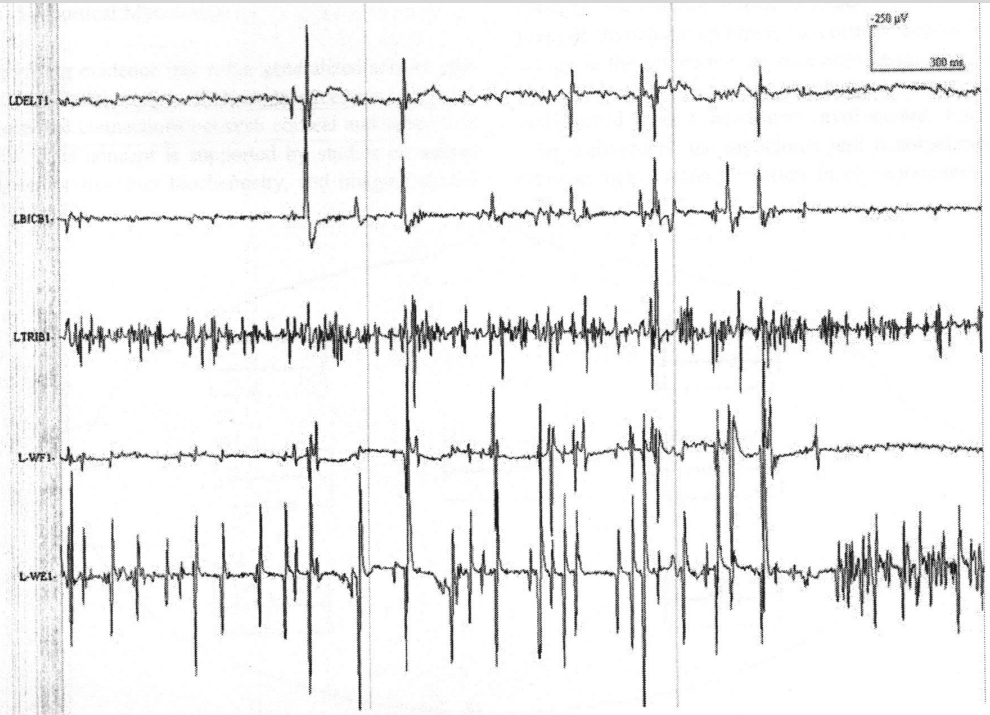
M. Borg

Unité des pathologies du mouvement, fédération des neurosciences cliniques, hôpital Pasteur, 30, avenue de La-Voie-Romaine, 06002 Nice cedex 01, France

Available online 17 January 2007

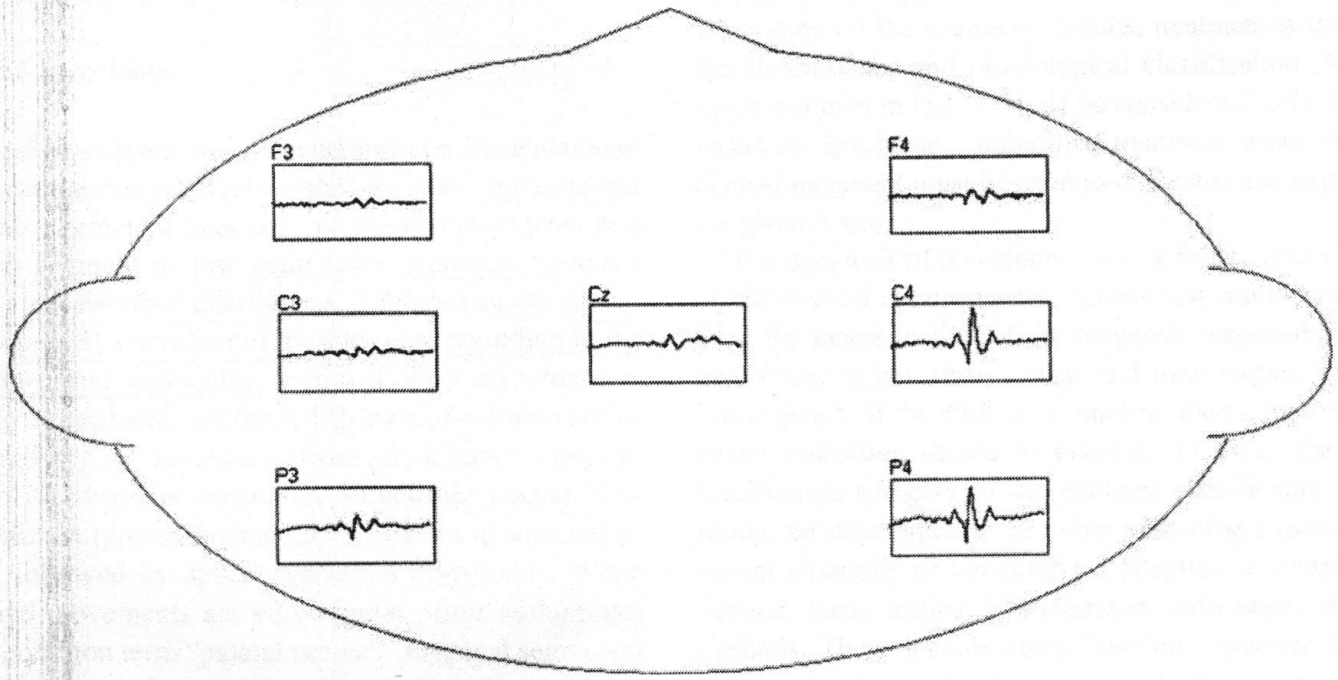
Mioclono corticale

- il più comune
- spesso multifocale, può anche essere focale, segmentario e generalizzato
- una breve e limitata attivazione corticale precede il mioclono con ridotta latenza < 40ms
- EEG: spike wavefom bifasiche o trifasiche con iniziale deflessione positiva che precede il mioclono, durata di 15-40ms, localizzazione nella corteccia sensitivo- motoria (elettrodi centrali e centro-parietali)
- conduzione nervosa: via piramidale, mioclono controlaterale
- EMG: contrazione simultanea di muscoli agonisti ed antagonisti


250 µV
300 ms
LDELT1
LBICB1
LTRIB1
L-WF1
L-WE1

EMG

EEG


F3
F4
C3
Cz
C4
P3
P4

TRATTAMENTO:

riduzione del drive eccitatorio e/o aumento dell'inibizione

LEVETIRACETAM E PIRACETAM: riduzione dell'ipereccitazione modulando flusso Ca e K
Levetiracetam 1000-3000 mg /die
Piracetam 2.4 – 21.6 gr

SODIO VALPROATO: aumento dell'inibizione tramite aumento della sintesi e riduzione della degradazione del GABA
1200-2000 mg

CLONAZEPAM: utile in aggiunta al levetiracetam o acido valproico

…zonisamide, primidone, fenitoina, carbamazepina…

Mioclono corticale-sottocorticale

- Alterazioni parossistiche bidirezionali di connessioni tra strutture cortico-sottocorticali
- Più spesso attivazioni muscolari diffuse e bilaterali, raramente focali o multifocali
- EEG: scariche veloci o lente di spike e onde
- EMG: durata uguale o più lunga del corticale, anche 100ms

TRATTAMENTO:
meccanismi GABAergici, colinergici, monoaminici
CLONAZEPAM
5-IDROSSITRIPTOFANO
…acido valproico, piracetam….

Mioclono subcorticale-non segmentale

- Attivazione muscolare rostrale e caudale del muscolo a genesi subcorticale
- L'attività corticale non si correla con il mioclono (EEG con spikes PESS allargati)
- Implicati gangli della base, tronco encefalico e cervelletto
- EMG: durata 200ms
- Può associarsi a quadri EEG di bust-suppression.

TRATTAMENTO:

CLONAZEPAM

…carbamazepina, lioresal, acido valproico, fenitoina….

Mioclono segmentale

- Generato a livello del tronco dell'encefalo o del midollo spinale
- Coinvolgimento di un segmento o alcuni segmenti vicini, clinica focale
- Attivazione muscolare persistente, ritmica dei muscoli corrispondenti ai segmenti attivati
- EMG: attività sincrona, ritmica o semiritmica muscolare, durata 50-500ms

Mioclono periferico

- movimenti a scatto a partenza periferica

…IL MIOCLONO POST-ANOSSICO…

Resuscitation 83 (2012) 265–269

Contents lists available at SciVerse ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Case report

Neurologic recovery after therapeutic hypothermia in patients with post-cardiac arrest myoclonus☆

Jason M. Lucas[a], Michael N. Cocchi[a,b], Justin Salciccioli[a], Jessica A. Stanbridge[a], Romergryko G. Geocadin[c], Susan T. Herman[d], Michael W. Donnino[a,e,*]

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CRITERI DIAGNOSTICI:

- ✓ Paziente in coma
- ✓ Mioclono continuo (spesso multidistrettuale), movimenti a scatto ritmici o irregolari e bilaterali del volto, tronco e arti, spesso con ripetitivi movimenti palpebrali, apertura degli occhi, rotazione degli occhi in alto e clonie buccali.
- ✓ Insorgenza precoce, entro 24 ore dall'insulto ipossico-ischemico

ARTICLE IN PRESS

ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2013; ■: ■ ■ ■ - ■ ■ ■

CLINICAL NOTE

Postanoxic Myoclonus: Two Case Presentations and Review of Medical Management

Adrian Budhram, BHSc, David Lipson, MD, Shanker Nesathurai, MD, MPH, FRCPC, David Harvey, MD, FRCPC, Michel P. Rathbone, MB, ChB, PhD, FRCPC

From the Divisions of Neurology and Physical Medicine and Rehabilitation, Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton Health Sciences, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.

Abstract

Postanoxic myoclonus is a rare manifestation after an anoxic event, with fewer than 150 cases reported in the literature. The condition is characterized by myoclonic jerks, which are worse on action than at rest, and postural lapses, ataxia, and dysarthria. The disability caused by postanoxic myoclonus can be profound, and treatment in the rehabilitation setting is exceptionally challenging. We present 2 patients who suffered from postanoxic myoclonus after an anoxic event, both of whom were successfully treated with a combination of levetiracetam, valproic acid, and clonazepam. These cases act as a framework for discussing the management of postanoxic myoclonus in the clinical setting.

Archives of Physical Medicine and Rehabilitation 2013; ■: ■ ■ ■ - ■ ■ ■

neurocritical care society Neurocrit Care (2012) 16:136–138

DOI 10.1007/s12028-011-9616-6

NEUROIMAGE

Ongoing Abdominal Status Myoclonus in Postanoxic Coma

Stephane Legriel · Marie-Benedicte Le Stang · Sybille Merceron · Pierrick Cronier · Gilles Troche

✓EEG:

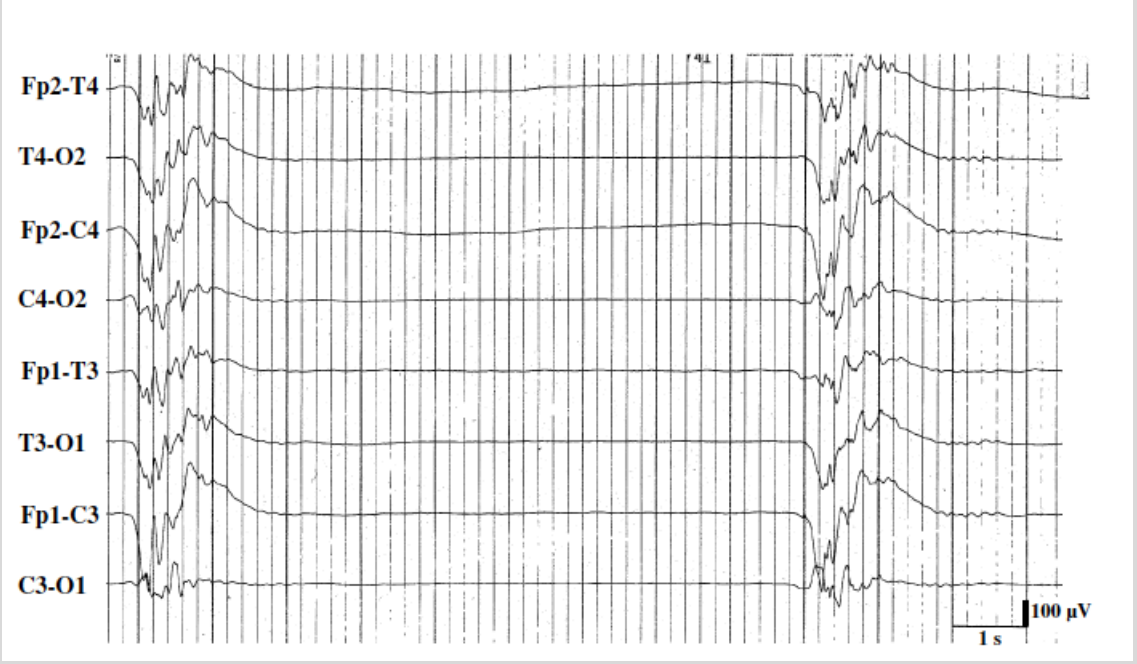
- presenza di spike-wave irregolari generalizzate o bilaterali, ma asimmetriche su un tracciato lento (definizioni: “non convulsivo” o stato epilettico “mioclonico” e mioclono sottocorticale)

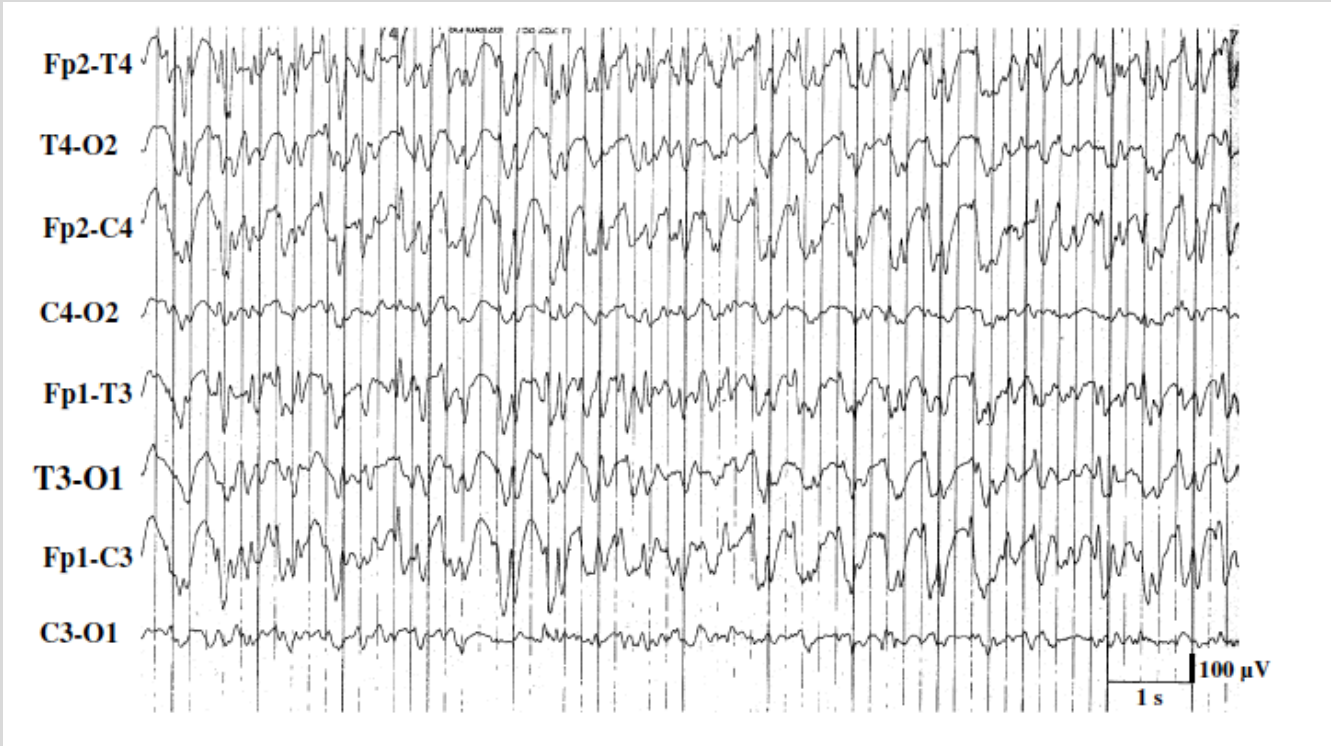
- bust suppression con spasmi in flessione degli arti che coincidono con i burst (genesi profonda, tronco dell’encefalo, prognosi peggiore, mioclono reticolare)

- nessuna correlazione EEG (mioclono sottocorticale)

“Carotid brainstem reflex myoclonus” è un mioclono reticolare, i movimenti mioclonici sono tempo-correlati con la pulsazione carotidea e scompaiono con il massaggio del nodo del seno.

Talvolta è necessario curarizzare il paziente per eseguire l’EEG per eliminare gli artefatti dati dalla clonie, si perde così la correlazione con EMG.


Fp2-T4
T4-O2
Fp2-C4
C4-O2
Fp1-T3
T3-O1
Fp1-C3
C3-O1
100 µV
1 s


Fp2-T4
T4-O2
Fp2-C4
C4-O2
Fp1-T3
T3-O1
Fp1-C3
C3-O1
100 µV
1 s

TERAPIA

- Non esistono regole o linee guida
- Pochi articoli, molti case report
- Sicuramente terapie polifarmacologiche
- Situazione temporanea

- Fenitoina 75mg+125mg, ac. Valproico 650mgx4, keppra 1500mgx2
- Ac. Valproico 500mgx3, levetiracetam 1500mgx2, clobazam 10mg
- Benzodiazepine al bisognoe a fiumi…
- Sedazione in pc con propofol fino a risoluzione del quadro (che fretta c'è…)
- Poco utile piracetam e levetiracetam in associazione.

Intensive Care Med (2011) 37:177–179
DOI 10.1007/s00134-010-2055-6

Marion Venot
Nicolas Weiss
Sophie Espinoza
Audrey Imbert
Jean-Marc Tadie
Jean-Yves Fagon
Emmanuel Guerot
Jean-Luc Diehl

Improvement of early diagnosed post-anoxic myoclonus with levetiracetam

Accepted: 26 July 2010
Published online: 25 September 2010

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-010-2055-6) contains supplementary material, which is available to authorized users.

was able to walk and speak, whereas the second one was not. However, in both cases, myoclonus had almost disappeared. Long-term evolution was good (Table 1). In our two cases, levetiracetam was highly effective. One patient was able to interrupt the treatment after 6 months and the second is still under decreasing dosage. We used the minimum dose of levetiracetam that controlled the myoclonus. As previously described, the dosage of levetiracetam is 1,000–4,000 mg/day in this condition [2]. Neither of our patients presented side effects, and these have only seldom been reported. Although some patients cannot be fully returned to health, treatment with levetiracetam seems to improve their quality of life.

Clinical/Scientific Notes

Frank Thömke, MD
Sacha L. Weilemann, MD

POOR PROGNOSIS DESPITE SUCCESSFUL TREATMENT OF POSTANOXIC GENERALIZED MYOCLONUS

Generalized myoclonus (GM) after cardiopulmonary resuscitation (CPR) implies a poor prognosis.[1] Postanoxic GM is usually classified as one type of convulsive status epilepticus,[2] which is also reflected by terms like myoclonic status,[3] myoclonic status epilepticus,[4] or postanoxic status epilepticus.[5] Antiepileptic drugs commonly used in the treatment of status epilepticus such as phenytoin or valproate, however, are ineffective in the majority of these patients.[3,4,6] Reports of single patients[7] and our own observations[6] indicated that propofol may control GM. This prompted us to use propofol as standard treatment of postanoxic GM in 60 consecutive comatose survivors of CPR.

Level of evidence. This is a single observational study without controls (Class IV).

Methods. We included 28 women, aged 26 to 87 years, mean age 58 years, and 32 men, aged 20 to 82 years, mean age 55 years. All were resuscitated due to cardiac arrest or ventricular fibrillation outside the hospital. None of the patients was treated with mild hypothermia. No patient had a history of epilepsy. All developed GM within 24 hours after CPR. GM always involved the facial muscles, shoulder, and proximal arm muscles. More than half of the patients also had jerks of the diaphragm. As there are numerous sources of acoustic stimuli on intensive care units, it is sometimes impossible to differentiate spontaneously occurring myoclonic jerks from those triggered by acoustic stimuli. Keeping this limitation in mind, about half of our patients had spontaneous myoclonic jerks, which increased on acoustic or somatosensory stimuli, and the other half myoclonic jerks on external stimuli (noise, pain, touch, tracheal suctioning).

All patients had bipolar 8-channel EEG recordings with needle electrodes positioned according to the standard 10–20 system (Fp2-T4, T4-O2, Fp2-C4, C4-O2, Fp1-T3, T3-O1, Fp1-C3, C3-O2). Filter setting was 0.53 Hz and 70 Hz. The first EEG (10 minutes) was done 6 to 24 hours after CPR when the patients had GM. During this recording, IV propofol was started with a single dose (1.5 mg/kg body weight). Efficacy was defined as cessation of GM and epileptiform EEG activity, i.e., absence of spikes and/or sharp waves intermixing the bursts in patients with a burst-suppression pattern (BSEEG), or spikes, polyspikes, sharp waves and sharp-slow waves in patients with continuous generalized epileptiform discharges (CGED).

The bolus injection of propofol was followed by continuous infusion (1 mg/kg body weight/h). The dose was individually adjusted to suppress GM; i.e., reappearance of GM prompted another bolus injection of 1 mg/kg body weight and an increase of continuous propofol by 20 mg/h. Necessity of propofol was reevaluated after 1 and 2 other days; i.e., 2 and 3 days after CPR. For that purpose, we discontinued propofol and performed another EEG (for 10 minutes) 1 hour after stopping propofol. The drug was stopped when GM had ceased and when the EEG was without epileptiform activity.

Serum neuron-specific enolase was determined 1, 2, and 3 days after CPR. Determinations regarding the level of care to be provided were made 4 days after CPR in all patients surviving up to this point.

Results. GM was associated with BSEEG (n = 39) or CGED (n = 21) without intervening background activity and without change on external stimuli (acoustic, pain). GM ceased immediately after a single dose of IV propofol in all patients, which also reliably suppressed epileptiform EEG activity (figure). Cessation of GM was maintained by continuous propofol infusion at individual doses between 80 and 250 mg/h.

Forty-one patients died within 3 days after CPR, leaving 19 surviving patients 4 days after CPR. At that time, each patient had 1) a serum neuron-specific enolase between 35 and 650 ng/mL at days 2 or 3 post-CPR, 2) 3 recordings of an unfavorable EEG pattern, i.e., BSEEG, CGED, flat (below 20 μV) or isoelectric (at 2 μV/mm) recordings, and 3) no motor response on painful stimuli. One third also had bilateral absence of the pupil light reaction or of the corneal reflex or both. Each of these findings predicts poor out-

come.[1] This was communicated with the families. Treatment was subsequently restricted to mechanical ventilation and IV fluids. Eighteen patients died during the following 10 days, and 1 survived in a persistent vegetative state.

Discussion. Propofol reliably controls postanoxic GM in comatose survivors of CPR. Epileptiform EEG activity of these patients was also suppressed. Successful treatment of GM, however, does not change the poor prognosis of these patients, which seems to be determined by the severity of the anoxic brain damage. (Preliminary and limited experiences indicate that this is also the case in patients with GM and/or CGED or BSEEG treated with mild hypothermia.)

Our observations do not contradict recent findings that single patients with postanoxic status epilepticus (PSE) may survive with mild or moderate

Predittori di outcome sfavorevole nei pazienti comatosi sopravvissuti ad ACC

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review article

Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A systematic review and meta-analysis. Part 1: Patients not treated with therapeutic hypothermia☆

Claudio Sandroni[a,*], Fabio Cavallaro[a], Clifton W. Callaway[b], Tommaso Sanna[c], Sonia D'Arrigo[a], Michael Kuiper[d], Giacomo Della Marca[e], Jerry P. Nolan[f]

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Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia☆

Claudio Sandroni[a,*], Fabio Cavallaro[a], Clifton W. Callaway[b], Sonia D'Arrigo[a], Tommaso Sanna[c], Michael A. Kuiper[d], Matteo Biancone[a], Giacomo Della Marca[e], Alessio Farcomeni[f], Jerry P. Nolan[g]

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[e] Department of Neurology, Catholic University School of Medicine, Rome, Italy
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[g] Department of Anaesthesia and Intensive Care Medicine, Royal United Hospital, Bath, UK

SCOPO: reviews sistematiche; valutano l'accuratezza di predittori precoci (< 7 gg) di ***outcome* sfavorevole** nei pazienti comatosi sopravvissuti ad ACC.

Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A sistematic review and meta-analysis. Part 1: patients non treated with therapeutic hypothermia. Sandroni C. et al. Resuscitation 84, 2013: 1310- 1323.
Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A sistematic review and meta-analysis. Part 2: patients treated with therapeutic hypothermia. Sandroni C. et al. Resuscitation 84, 2013: 1324- 1338

CEREBRAL PERFORMANCE CATEGORIES (CPC)

1. **Good cerebral performance**

Conscious: alert, able to work and lead a normal life. May have minor psychological or neurological deficit (mild dysphasia, nonincapacitating hemiparesis or minor cranial nerve abnormalities)

3. **Moderate cerebral disability**

Conscious. Sufficient cerebral function for part-time work or indipendent activities of daily life.may have hemiplegia, seizures, ataxia…

3. **Several cerebral disability**

Conscious. Dependent on others for daily support because of impaired brain function. Limited cognition. Includes a wide range of cerebral abnormalities

4. **Coma, vegetative state.**

Not conscious. Unaware of surroding, no cognition. No verbal or phychological interaction with environment.

5. **Death**

Certified brain death or dead by traditional criteria.

PAZIENTI:

- popolazione adulta ≥ 16 aa
- in coma dopo ACC (GCS ≤ 8)
- esclusi pazienti in coma anossico non da ACC

Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A sistematic review and meta-analysis. Part 1: patients non treated with therapeutic hypothermia. Sandroni C. et al. Resuscitation 84, 2013: 1310- 1323.
Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A sistematic review and meta-analysis. Part 2: patients treated with therapeutic hypothermia. Sandroni C. et al. Resuscitation 84, 2013: 1324- 1338

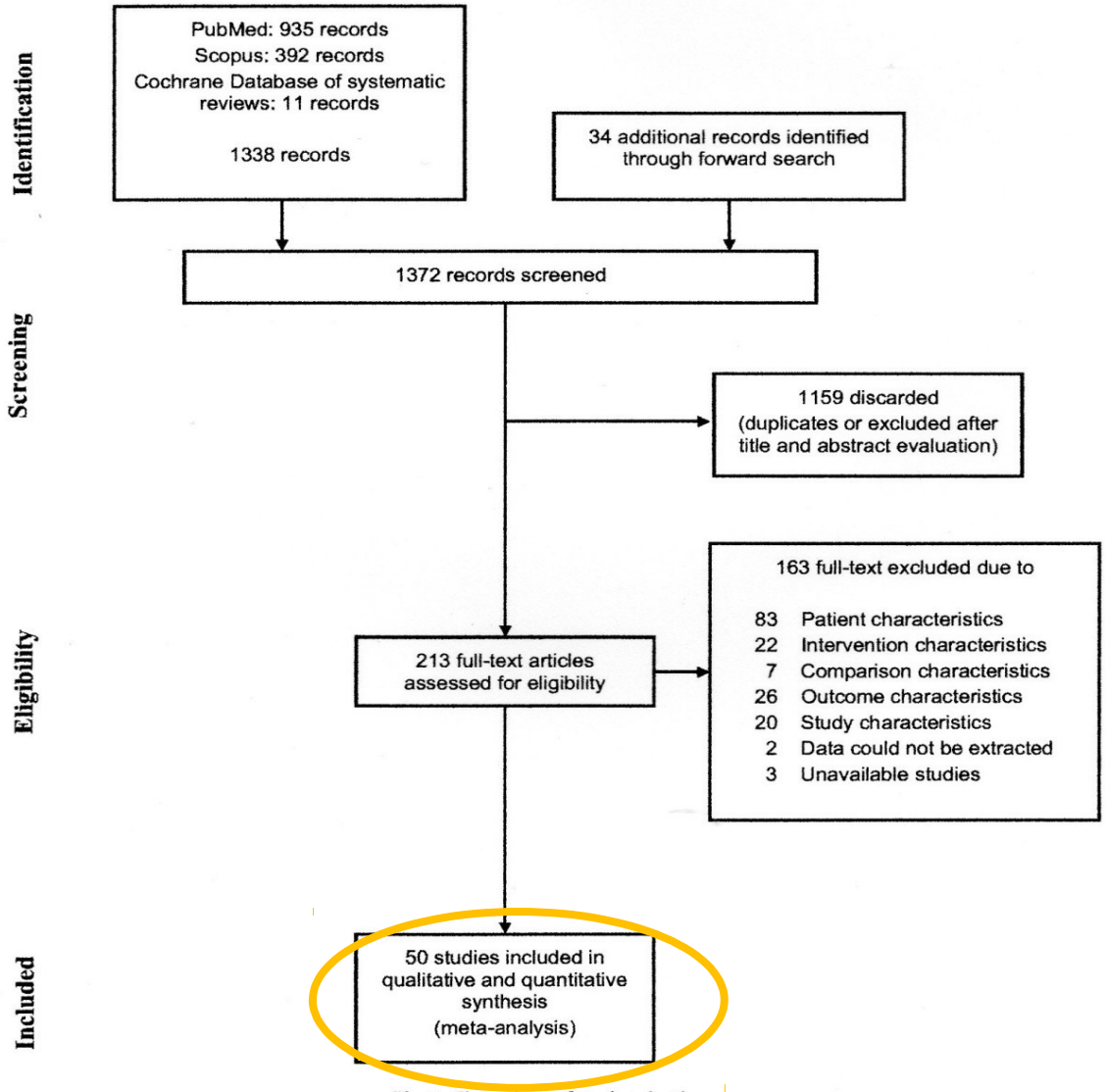

Fig. 1. Flow-chart of study selection.

Part 1: patients not treated with therapeutic hypothermia (2828 patients)

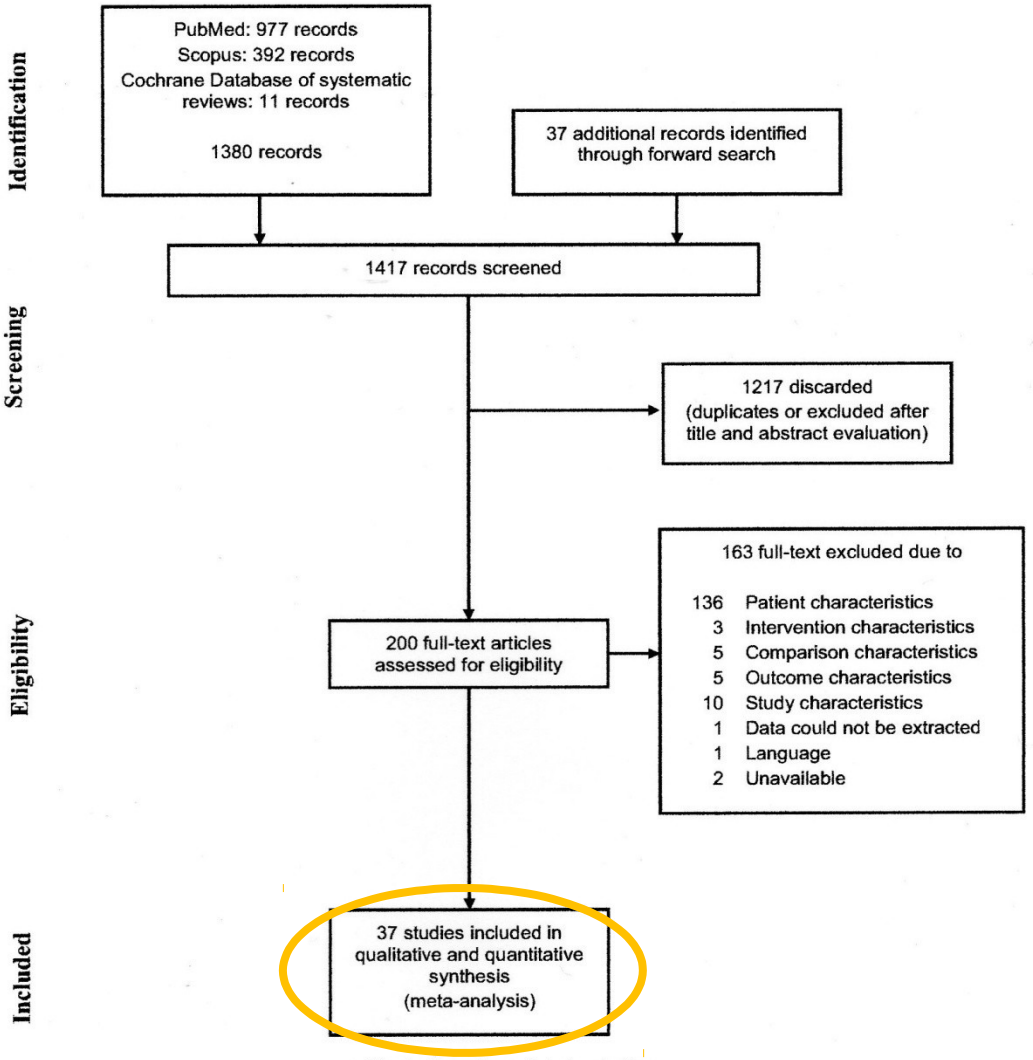

Fig. 1. Flow-chart of study selection.

Part 2: patients treated with therapeutic hypothermia (2403 patients)

PREDITTORI

- Esame clinico: riflessi di tronco, GCS, presenza di mioclono.
- Elettrofisiologia: EEG e PESS
- Biomarkers: NSE e S100B
- Imaging: TAC, RMN

Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A sistematic review and meta-analysis. Part 1: patients non treated with therapeutic hypothermia. Sandroni C. et al. Resuscitation 84, 2013: 1310- 1323.
Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: A sistematic review and meta-analysis. Part 2: patients treated with therapeutic hypothermia. Sandroni C. et al. Resuscitation 84, 2013: 1324- 1338

ESAME CLINICO: riflessi di tronco

Part 1: NON IPOTERMIA

- Assenza riflesso pupillare predice morte o stato vegetativo con 0% FPR non prima delle 72h
- Assenza riflesso corneale: non ottiene 0%FPR neanche a 72h. Combinazione con RFM non aumenta accuratezza

Part 2: IPOTERMIA

Assenza riflesso pupillare:

- all'ingresso: predittore non accurato (32% FPR)
- A 72 h o dopo, associato a poor outcome (0%)

Assenza riflesso corneale a 72h o dopo non è predittore accurato (FPR 0-5%)

ESAME CLINICO: mioclono

Part 1: NON IPOTERMIA

- Presenza di mioclono o stato di mioclono, registrati all'ingresso, predicono CPC 4-5 con 0% FPR.

Rimangono predittivi durante le prime 72 h con alta precisione e bassa sensibilità (8-9%).

Part 2: IPOTERMIA

- 2 studi: tutti i pazienti con mioclono muoiono o rimangono in stato vegetativo. Registrato da 1 a 144h dopo ACC.
- 6 studi: presenza di mioclono entro le 72h non esclude buon recupero (FPR 5%).

ESAME CLINICO:
GCS o motor score

Part 1: NON IPOTERMIA

- Nessun valore di GCS o GCS motor score predice CPC 4-5 con 0% FPR

Part 2: IPOTERMIA

- 6 studi: motor score ≤2 dopo riscaldammento compatibile con buon recupero
- 1 studio: M≤2 e assenza RFM a 72h predicono poor outcome con 0% FPR

ELETTROFISIOLOGIA: PESS

Part 1: NON IPOTERMIA

- Assenza bilaterale di N20 predice morte o stato vegetativo con 0% FPR (da 1 a 8h da ACC)
- Rimane predittivo durante le prime 72 h con sensibilità 45-46%
- 1studio (159pz):assenza bilaterale di N20 a 48h predittore di CPC 3-5 con 0%FPR

Part 2: IPOTERMIA

- predittore più accurato di poor outcome
- Non influenzato da sedativi/ipotermia
- 4 studi: assenza bilaterale di N20 durante ipotermia predice accuratamente CPC 3-5 FPR 0%

BIOMARKERS

Part 1: NON IPOTERMIA

- Valori non definiti, timing non definito

Part 2: IPOTERMIA

- Valori non definiti
- Offrono vantaggi teorici (sono indipendenti dall'utilizzo di sedativi)
- Ma ampia variabilità dovuta a fonti extracerebrali/uso di tecniche di misura immunoenzimatiche eterogenee

ELETTROFISIOLOGIA: EEG

Part 1: NON IPOTERMIA

- EEG alpha coma: non associato in modo consistente a outcome sfavorevole (possibile induzione da barbiturici, oppioidi e BNZ)
- Presenza di EEG a basso voltaggio predice poor outcome con 0% FPR e alta precisione

Part 2: IPOTERMIA

- EEG non reattivo/burst suppression dopo riscaldamento predice accuratamente outcome sfavorevole
- Sebbene questo pattern durante TH è compatibile con un buon recupero

CONCLUSIONI

Part 1: NON IPOTERMIA

- Presenza di mioclono
  - non frequente
  - manca la definizione
  - predittore precoce con elevata specificità

Part 2: IPOTERMIA

- Stato di mioclono e stato epilettico hanno alta specificità
- Non raggiungono lo 0% di FPR
- Possono essere considerati predittori importanti,

MA pochi studi e manca definizione comune

CONCLUSIONI:
predittori di poor outcome

Part 1: NON IPOTERMIA

- Presenza di stato di mioclono a 24-48h
- assenza bilaterale di N20 (24-48h)
- assenza di attività EEG a 24-72h
- assenza di RFM a 72h
- (NSE predittore di poor outcome, non definito il valore)

Predittori con 0% FPR

Part 2: IPOTERMIA

- Burst suppression durante TH o dopo il riscaldamento
- Assenza bilaterale di N20 durante TH
- Assenza RFM e corneale con M≤2 a 72h
- NSE ≥81.8µg (48h)
- S100b ≥0.3µg (48h)

How to assess prognosis after cardiac arrest and therapeutic hypothermia

Fabio Silvio Taccone[1*], Tobias Cronberg[2], Hans Friberg[3], David Greer[4], Janneke Horn[5], Mauro Oddo[6], Sabino Scolletta[7] and Jean-Louis Vincent[1]

Abstract

The prognosis of patients who are admitted in a comatose state following successful resuscitation after cardiac arrest remains uncertain. Although the introduction of therapeutic hypothermia (TH) and improvements in post-resuscitation care have significantly increased the number of patients who are discharged home with minimal brain damage, short-term assessment of neurological outcome remains a challenge. The need for early and accurate prognostic predictors is crucial, especially since sedation and TH may alter the neurological examination and delay the recovery of motor response for several days. The development of additional tools, including electrophysiological examinations (electroencephalography and somatosensory evoked potentials), neuroimaging and chemical biomarkers, may help to evaluate the extent of brain injury in these patients. Given the extensive literature existing on this topic and the confounding effects of TH on the strength of these tools in outcome prognostication after cardiac arrest, the aim of this narrative review is to provide a practical approach to post-anoxic brain injury when TH is used. We also discuss when and how these tools could be combined with the neurological examination in a multimodal approach to improve outcome prediction in this population.

Taccone S.et al. How to assess prognosis after cardiac arrest and therapeutic hypothermia. Crit Care 2014; 18: 202.

SCOPO: review sistematica. Fornire approccio pratico multimodale da applicare ai pazienti comatosi sopravvissuti ad ACC e sottoposti a TH.

Taccone S.et al. How to assess prognosis after cardiac arrest and therapeutic hypothermia. Crit Care 2014; 18: 202.

Esame clinico

- Non TH: M≤ 2, assenza bilaterale di riflesso fotomotore e corneale a 72h predittori di outcome sfavorevole.

- ✓ TH può prolungare il metabolismo dei farmaci, ciò può ridurre il valore predittivo dell'esame clinico <72h.
- ✓ Informazioni prognostiche legate solo ad una minoranza di pz (perdita di riflessi di tronco/asimm pupillare)
- ✓ EEG e neuroimaging possono esser usati per confermare danno cerebrale esteso o swelling.

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GCS e MIOCLONO

Con la sospensione dei sedativi, durante il riscaldamento:

- GCS ≥5: non richiede indagini aggiuntive
- GCS ≤4: considerare indagini aggiuntive
- GCS≤ 2: da solo(in III giornata) predittore di outcome sfavorevole con FPR 12-24 % , se associato ad assenza di riflessi di tronco o con mioclono: FPR 4%.

- Mioclono generalizzato (faccia, gambe)è spesso associato a burst suppression all'EEG.
- Segno infausto se presente nelle prime 24 h o se ha durata > 30 min (stato epilettico). Per essere predittore di outcome infausto va associato a assenza bilaterale di N20 .

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EEG

Definiti pattern maligni/benigni: stato epilettico postanossico, alpha coma, burst suppression.

EEG non reattivo: definito come l'assenza di qualsiasi cambiamento sotto stimolazione, è significativamente associato a morte.

Ha valore predittivo migliore per definire outcome neurologico rispetto ai pattern maligni/benigni e ai PESS.

EEG: va sempre associato ad esame neurologico a 48-72h.

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PESS

Non influenzati da alterazione del metabolismo o dai farmaci sedativi(propofol riduce l'ampiezza del 10%; midazolam/oppioidi effetto minimo sull'ampiezza/latenza).

- Non TH: assenza bilaterale N20 al I-III gg predice outcome sfavorevole. Possibili falsi positivi se eseguiti precocemente < 24h.
- TH: assenza bilaterale di N20 (II-III gg) predice outcome sfavorevolecon 0% FPR. La presenza di N20 non implica buon recupero.

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APPROCCIO MULTIMODALE

- **Non TH**: NSE, GCS, PESS aumentano la prevedibilità di outcome infausto dal 64 al 76%.

- Combinazione di esame neurologico, EEG e PESS e due biomarkers migliorano il valore prognostico, non falsi positivi.

- **TH**: PESS, NSE, EEG aumentano il numero dei pazienti identificati come outcome sfavorevole dal 75 al 88%.

Taccone S.et al. how to assess prognosis after cardiac arrest and therapeutic hypothermia. Crit Care 2014; 18: 202.

APPROCCIO MULTIMODALE

1. EEG patterns vanno correlati all'esame clinico a 48-72 h dopo la sospensione della TH.
2 .Presenza di stato mioclono durante le prime 24h, può predire outcome sfavorevole se associato ad assenza bilaterale di N20 dopo riscaldamento.
3.possibile ipotizzare outcome sfavorevole se: assenza di riflesso pupillare/corneale e M≤2 in III giornata. Accuratezza prognostica aumenta se questi segni sono associati a EEG non reattivo/pattern maligni.

Taccone S.et al. how to assess prognosis after cardiac arrest and therapeutic hypothermia. Crit Care 2014; 18: 202.

CONCLUSIONI

- ✓ Prognosi accurata ottenuta solo dalle 72 alle 96 ore dopo ACC e richiede un approccio multimodale
- ✓ Esame neurologico rimane il gold standard (ritardo nella risposta motoria nei pazienti sottoposti a TH
- ✓ EEG: fornisce maggiore accuratezza (EEG non reattivo/ burst suppression sono associati a outcome sfavorevole)
- ✓ Assenza bilaterale di N20 a 48-72h è associato a poor outcome
- ✓ Biomarkers: forniscono informazione sulla severità del danno, mai utilizzati da soli
- ✓ RMN: può identificare pazienti con danno ipossico esteso

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SEMPRE LO STESSO MIOCLONO NEL PAZIENTE PRIMA IN COMA E POI SVEGLIO?

MIOCLONO DIFFERENTE?

Myoclonus after cardic arrest

- The survivors of cardiac arrest may develop post-hypoxic myoclonus (PHM).
- Two types of PHM can occur in patients with hypoxic injury of the brain: the acute and the chronic.
- **The acute PHM**, also termed post-hypoxic myoclonic status epilepticus (MSE), occurs soon after a hypoxic insult and is characterized by generalized myoclonic jerks in patients who are deeply comatose.
- **The chronic PHM**, also known as Lance-Adams syndrome (LAS), is predominantly characterized by action myoclonus that starts days to weeks after cardiorespiratory resuscitation (CPR) in patients who regained consciousness.

LANCE-ADAMS SYNDROME

The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy.

Lance, J.W., Adams, R.D.

Brain 1963, 86(1):111-136.

INTRODUCTION

- In 1963, James Lance and Raymond Adams described a syndrome of intention or action myoclonus, seen in four survivors of cardiorespiratory arrest.
- After a period of cerebral hypoxia they developed myoclonic jerks which were often accompanied by a cerebellar syndrome and mild cognitive impairment, typically occurring days to weeks after the event.
- Lance-Adams syndrome is a rare complication and a few than 150 cases have been reported in the literature.

CHARACTERISTICS

- Action myoclonus.
- Occurs in patients after they have regained consciousness days to weeks after CPR.
- No consistent correlation with EEG abnormalities.
- The myoclonic jerks are specifically triggered by action, startle, and tactile stimulation.
- Usually disappear with relaxation of the body and limbs or with a sleep.
- The severity of the myoclonus is proportional to the precision of the task that is required

PATHOPHYSIOLOGY

- The pathophysiology of LAS is elusive, but the mechanism of hypoxic brain injury has been assumed to be an important role.
- In cases of LAS there is usually a documented period of hypoxia preceding hypoxic cardiac arrest, such as cases of severe asthma or airway obstruction.
- The brain injury in cardic arrest following hypoxia has been shown to differ from that occuring in sudden circulatory arrest secondary to cardic dysrhythmias.

PATHOPHYSIOLOGY

- Ferlazzo et al (2013) hypothesized that a transient cerebral hypoxia may provoke a permanent synaptic rearrangements of the neuronal networks involved in the pathogenesis of post-hypoxic myoclonus.

- The repetitive firing of thalamo-cortical fibers arising from the ventrolateral nucleus, which is the main relay nucleus from the cerebellum to the sensory-motor cortex, has been proposed as the main mechanisms of myoclonus in LAS.

- Several lines of evidence suggest that post-hypoxic myoclonus may be due to synaptic dysfunction with chemical imbalances of neurotransmitter systems and in particular of serotoninergic pathways.

PATHOPHYSIOLOGY

- Loss of neurotransmitter serotonin (5-hydroxytryptophan, 5-HT) within the inferior olive.

- Other neurotransmitter systems, such as gamma-aminobutyric acid (GABA), may also be involved and interact with the 5-HT system to suppress PHM.

PATHOPHYSIOLOGY

- Welsh et al. considered that certain brainstem structures, the paravermal and vermal areas of the cerebellum, and the diencephalons may be implicated in human PHM.
- The loss of GABAnergic inhibition in cerebellar afferent neurons after ischemia leads to diaschisis of the motor thalamus and reticular formation, which, in turn, is responsible for enhanced motor excitability and myoclonus.

PATHOPHYSIOLOGY

- Dubinsky et al.(1991) demonstrated a significant increase in the metabolism of the medulla in patients with palatal myoclonus, presumably due to hypertrophy of the inferior olivary nucleus, which is said to possess intrinsic pacemaker properties.
- Using PET scan, Frucht et al.(2004) reported that, compared with control subjects, 7 patients with LAS had significantly increased glucose metabolism in the pontine tegmentum, spreading to the mesencephalon and the ventrolateral thalamus.

NEUROIMAGING

- Diagnostic imaging tests such as CT or MRI of the brain are not helpful to make a diagnosis of LAS.

- Ferlazzo et al. demonstrated a transient thalamic and cerebellar involvement with no permanent anatomic brain damage as demonstrated by advanced MRI analysis and probably due to reversible cytotoxic edema.

- Neuroimaging, such as brain SPECT or brain positron emission tomography (PET), has showed the anatomical and pathophysiological basis of LAS.

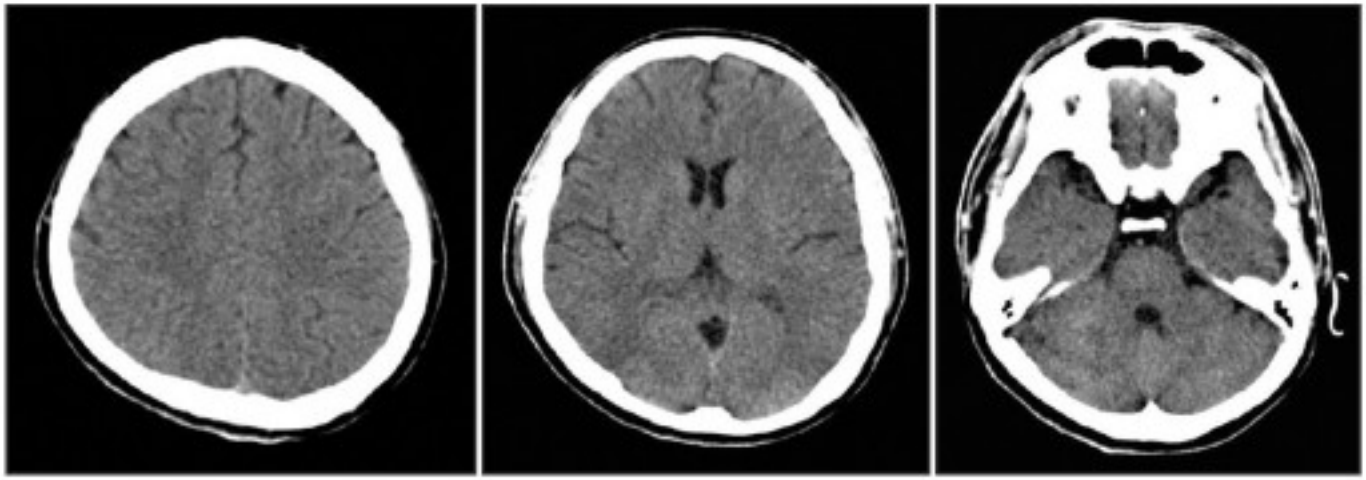

Fig. 1. The brain computed tomography scan shows normal findings.

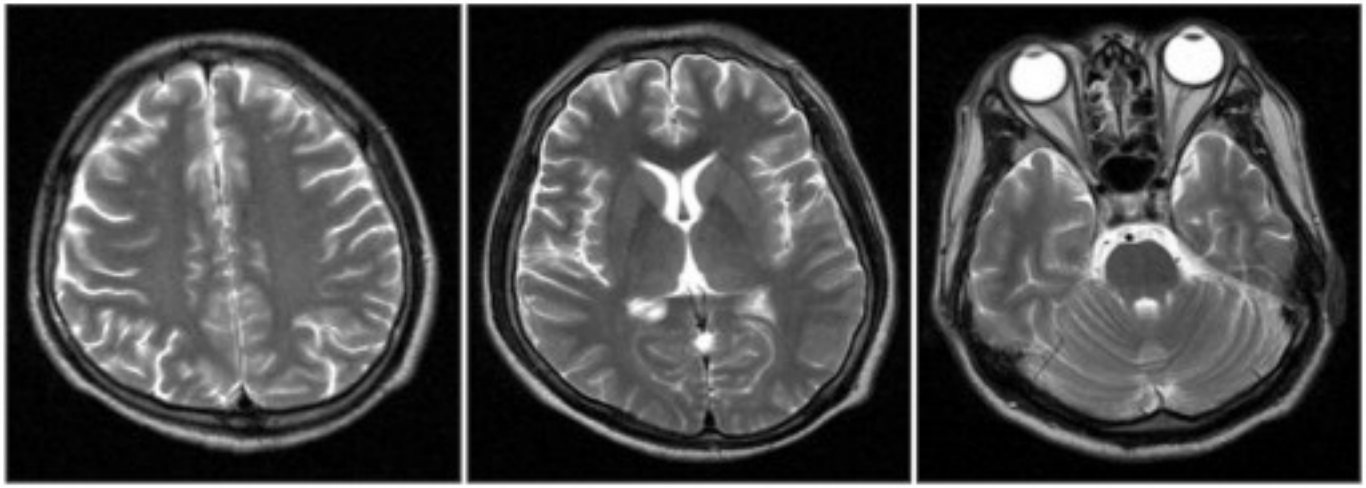

Fig. 2. The T2-weighted images of brain magnetic resonance imaging show mild diffuse brain atrophy.

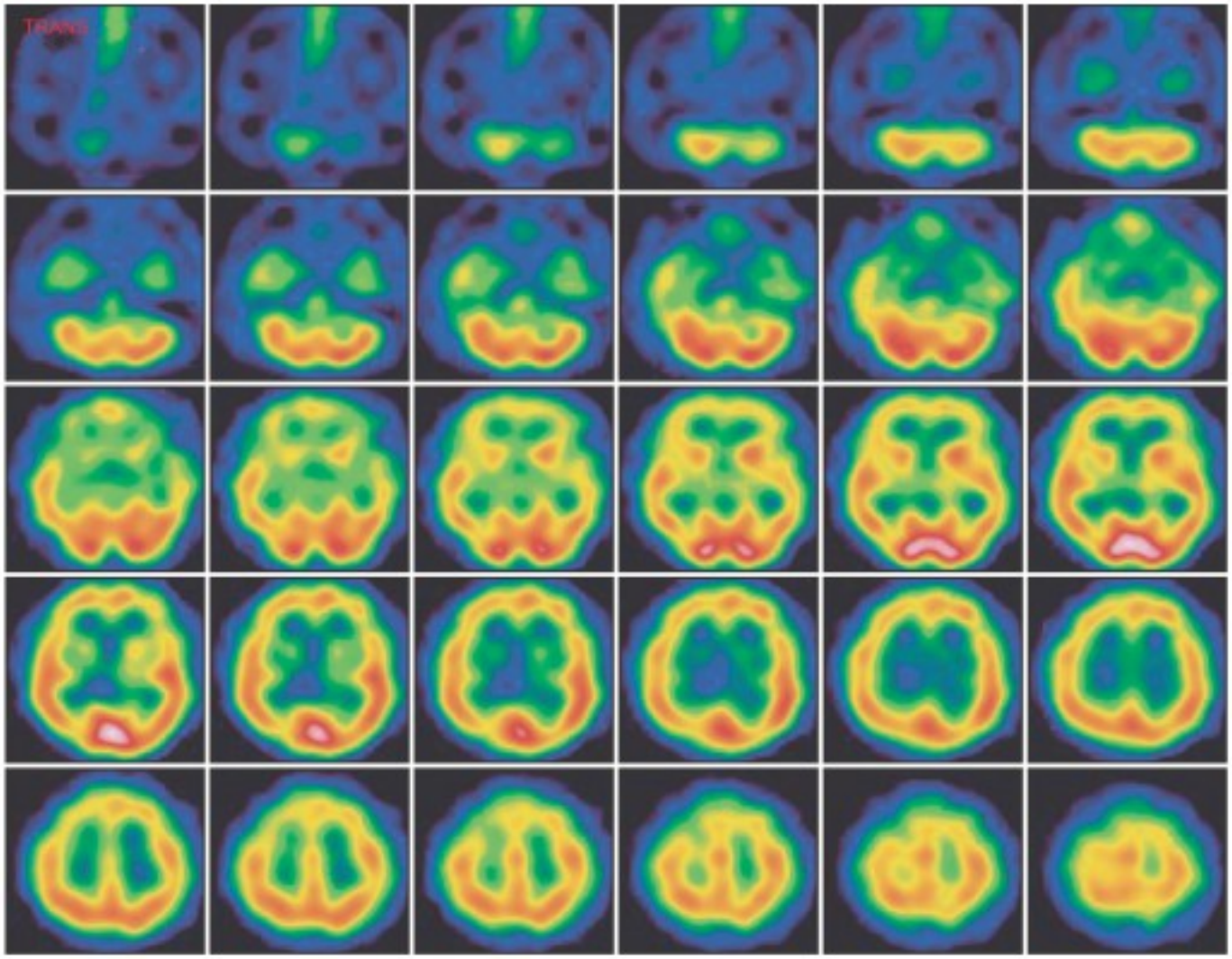

Fig. 3. The brain single photon emission computed tomography scan shows mild diffuse hypoperfusion in the brain and especially in the right basal ganglia and left temporal region 1 month after cardiorespiratory resuscitation

PROGNOSIS

- Lance–Adams syndrome is normally associated with survival with preserved intellect, with or without chronic myoclonus and cerebellar problems.
- The degree to which chronic intention myoclonus associated with Lance–Adams syndrome affects normal activities of daily living has been reported to vary, but amongst published cases there is a high proportion of patients who were unable to independently mobilize, wash, dress, feed themselves or return to work.

TREATMENT

- The treatment of LAS has not been established and a combination of medications based on the neurotransmitters has been reported.
- Frucht and Fahn (2000) reviewed more than 100 patients with LAS and they found that clonazepam, valproate, and piracetam were effective in treating approximately 50% of the cases.
- Polesin and Stern (2006) recommended levetiracetam, zonisamide, clonazepam, and valproate as the first treatments of choice.
- 5-HTP (5-Hydroxytryptophan) seems to be of benefit in resistant cases.

DIFFERENTIAL DIAGNOSIS

Table 1 Distinguishing features of myoclonic status epilepticus and Lance–Adams syndrome.

	Myoclonic status	Lance–Adams syndrome
Conscious level	Comatose	Aware, caution re sedation
Time course	Within 12–24 h, stopping after 24 h	Later onset, may become chronic
Myoclonus	Generalised, multifocal	Usually intention myoclonus
Prognosis	Extremely poor	Normally preserved intellect, +/− chronic myoclonus
Pathophysiology	Ischaemic brain injury with neuronal necrosis	Hypoxic brain injury without irreversible infarction

CONCLUSION

- Failure to recognize LAS may result in inappropriate anticonvulsant therapy and delayed treatment.
- Therefore, when a patient develops uncontrolled myoclonus after CPR and regaining consciousness, and the myoclonus is unsuccessfully treated with traditional anticonvulsants for a certain period, the possibility of LAS should be considered.
- This can lead to minimizing the patient's disabilities and improving the prognosis.